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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,048	HEINZ ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDO

DETAILED ACTION

Receipt is acknowledged a corrected Appeal Brief, filed 7/13/2005. Subsequent to an Appeal Conference and upon careful review of the claims, prosecution in this case is re-opened, because new grounds of rejection are applicable.

Claims 1-12 are pending and claims 11-12 are withdrawn from consideration pursuant to a restriction requirement of record (mailed 09/03/2003). The version of the claims pending is that which was filed on 04/19/2004 (a copy of which is also submitted in the Appendix of the Appeal Brief). Where applicable, a response to Applicant's arguments is set forth immediately following the body of any rejection set forth herein. Claims 1-10 are under consideration in this action.

Claim Objections

Claim 1 objected to because of the following informalities:

Claim 1 recites the term "this organism" which is not indefinite *per se*. However, in the interest of consistency throughout the claims, the term "this" should be replaced with "the". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. **Claim 9 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.**

This is a new ground of rejection. The claim is directed to a transgenic organism, including animals. The specification indicates that "transgenic organisms" are to be understood as ones containing a foreign nucleic acid and include animals. (e.g., p. 23, ll. 15-35). In other words, the claims read on the whole animal. Therefore, since human beings are animals, the claim reads on transgenic humans (i.e., whole animal organism that is a human). As such the claim is improperly directed to non-statutory subject matter – transgenic humans.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. **Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Independent claim 1 recites the limitation "substantially reducing" which does not appear to be particularly defined in the specification (e.g., as to degree or reference point). As such the limitation is a relative term. For example, one of skill would not know whether 10% or 51% each constitutes a "substantial reduction". Thus, the claims' metes and bounds are indeterminable.

In addition, claim 1 recites the term "the enzymatic action of the polypeptides", which lacks sufficient antecedent support. It would be remedial to replace "the enzymatic action" with "the Δ6-desaturase activity" (D6D), if this is what is intended.

Given the ambiguity, claim 1 is also vague and indefinite, because it is unclear how the limitation "enzymatic action" is to be interpreted. The specification does little to clarify said ambiguity, i.e., whether "enzymatic action" is the same as, or exclusive of D6D activity. For example, the specification explicitly states that multiple "enzymes" are encoded by SEQ ID NO: 1 thus implying that additional and exclusive "action" or activity is contemplated (e.g., p. 6, l. 32). As written, the claims are vague and indefinite.

Claims 2 and 3 recite the limitation "the nucleic acid sequence" when referring to claim 1. As written, it is unclear to which sequence the claims are delimited. For example, the dependent claims can be directed to individual members of the Markush group of nucleic acid sequences recited in independent claim 1. Alternatively, the claims can be interpreted as directed to the "isolated nucleic acid", which is of different scope as compared to the preceding interpretation. For example, it is unclear whether "plant or algae" or "Physcomitrella patens" is directed to one of the three specific nucleic acids in claim 1 or to all the nucleic acids. It would be remedial to insert the term "isolated" before "nucleic acid" in claims 2 and 3, if this is what was intended.

Claim 4 is vague and indefinite, because it is unclear how an animal can be a cultured organism. More particularly, claim 4 depends from claim 1, which is directed to the introduction of a nucleic acid into an organism that is "cultured". The term "cultured" or "culturing" is not particularly defined in the specification, but even in the broadest reasonable interpretation, it is unclear how an animal is "cultured". While, microbial cells, or animal cells in culture may be "cultured", whole animals are not characterized as being "cultured". Thus, as written the claim's metes and bounds are indeterminable.

Claim 9 recites the limitation "Δ6 desaturase action", which lacks sufficient antecedent support, where the preamble recites the limitation "Δ6 desaturase activity". For example, the step of protein-protein binding could be interpreted as an "action" while the term "activity" is more readily construed as a function attributed to an enzyme such as the D6D.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

This rejection is of record and repeated herein, but supplemented with additional analysis not of record, so as to clarify the grounds of rejection. A response to Applicant's arguments is set forth immediately following the body of the rejection (infra, Response to Arguments). The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's invention is drawn to a process of preparing unsaturated fatty acids and to transgenic organisms, wherein the process utilizes or the organisms comprise at least one isolated nucleic acid of a sequence encoding a polypeptide with Δ6-desaturase (D6D) activity that is selected from the nucleic acid of SEQ ID NO: 1 (isolated from *Physcomitrella patens*), as well as nucleic acids that are derivatives of SEQ ID NO: 1 in the context of degeneracy of the genetic code where said derivatives encode a polypeptide of any size having the requisite D6D activity.

Thus, the claims encompass a genus of nucleic acids that are derivates of SEQ ID NO: 1 and that encode any polypeptide having D6D activity. In addition, the claims encompass a genus of nucleic acid derivatives of SEQ ID NO: 1 which encode any polypeptide with an amino acid sequence having at least 85% homology to any of the "amino acid sequences shown in SEQ ID NO: 2", and without substantially reducing an enzymatic action[1] or D6D activity. The specification defines the limitation "derivatives" to mean "functional homologues of the enzyme encoded by SEQ ID NO: 1 or their enzymatic activity, that is to say which catalyze the same *enzymatic reactions* as those of SEQ ID NO: 1". (emphasis added) (Specification, p. 6, ll. 31-35). Based on this definition, multiple undefined enzymatic activities are attributed to the polypeptide encoded by SEQ ID NO: 1 (i.e., SEQ ID NO: 2).

Therefore, the claims encompass a genus of nucleic acid molecules that encode *any polypeptide* of *any length* derived from SEQ ID NO: 1 that corresponds to Δ6-desaturase activity in *any* organism. In addition, the claims are directed to a subgenus of nucleic acids that encode *any polypeptide* of *any length*, which nucleic acids are derived from SEQ ID NO: 1, and that encode any polypeptide having at least 85% homology at the amino acid level to "the amino acid sequences shown in SEQ ID NO: 2", where said polypeptides must have the requisite Δ6-desaturase activity and where an "enzymatic action" of said polypeptide is not substantially reduced in any organism.

Notably, the limitation for 85% homology is not directed to the entire length of the polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

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[1] As noted in Rejection No. 2, it is unclear whether "enzymatic action" refers to Δ6-desaturase or other enzymes, but in the interest of advancing prosecution, the term "enzymatic action" (claim 1) is interpreted to mean D6D activity.

Rather, as written, the subgenus of nucleic acids is directed to any size sequence encoding any polypeptide that is at least 85% homologous to any amino acid sequence shown in SEQ ID NO: 2. In other words, as written the recited % homology can be over any localized region within SEQ ID NO: 2.

The nucleic acid sequence of SEQ ID NO: 1 consists of 2012 nucleotides, which corresponds to the 525 amino acid residues of SEQ ID NO: 2. Therefore, the number of potential embodiments for nucleic acids derivatives that are encompassed in the preceding genus/subgenus is tremendously large (any derivative of any size having the requisite activity or any derivative sharing at least 85% identity over any portion of SEQ ID NO: 2). In addition, the number of embodiments is further magnified by the fact that as written, claim 1 appears to be directed to derivatives encoding polypeptides having additional "enzymatic action", exclusive of D6D activity. Thus, the written description requirement requires a sufficient and representative number of embodiments to be disclosed or to be conventional in the art.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966). Therefore, to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed.").

Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572, 41 USPQ2d at 1966. Furthermore, the Guidelines for Written Description state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). The critical or essential features in the context of the instant claims are nucleic acid derivatives of SEQ ID NO: 1 that encode the necessary functional motifs having the requisite enzymatic activity.

The instant disclosure does not describe or identify said necessary structures within SEQ ID NO: 1 or any structural domains/motifs that is common to said derivatives and sufficient for D6D activity. Indeed, other than the full-length cDNA and corresponding amino acid sequence, not a single representative embodiment of the aforementioned genus or subgenus of nucleic acid molecules is identified in the specification. Thus, the only embodiment disclosed is the moss Δ6-desaturase, which is transformed into *A. thaliana* and oil seed rape plants. (e.g., p. 31, Example8). In other words, a representative number of embodiments of derivates is not disclosed, whereby said derivates are identified as resulting from the degeneracy of the genetic

code as corresponding to SEQ ID NO: 1, and wherein the derivatives encode polypeptide of any size having the requisite enzymatic activity.

Put another way, the disclosure fails to identify a structure to function correlation with respect to derivatives of any size encoding functional polypeptides or derivatives of any size that are 85% homologous to any polypeptide fragment encompassed by the moss Δ6-desature (i.e., SEQ ID NO: 2). Moreover, merely limiting nucleotides to encoding polypeptides having 85 percent homologous regions and that are delimited to having enzyme(s) functions, where said sequences have not been clarified, does not meet the written description requirement.

As noted above, the nucleic acid derivatives are directed respectively to nucleic acid encoding any polypeptide relative to any sequence of any size shown in SEQ ID NO: 2. Thus the disclosure is not descriptive of the complete structure of a sufficient number or a representative number of species, which the claims encompass, because one of ordinary skill in the art cannot envision all derivative or homologous sequences having the prescribed function, based on the teachings in the specification.

In sum a representative number of species has not been disclosed with respect to the genus/subgenus of nucleic acids encompassed by the claims, where such a disclosure must be sufficient to convince the skilled artisan that applicant is in possession of the claimed genus.

Response to Argument

Applicant's arguments filed 07/13/2005 (Appeal Brief; hereinafter Brief) have been fully considered but they are not persuasive. Applicant asserts that the disclosure meets the written description requirement because methods are known in the art for determining a given sequence based on homology.

More particularly, Applicant asserts that a computer algorithm may be utilized to determine sequences with the recited degree of sequence homology. (e.g., Brief, p. 3, last paragraph). Further, Applicant asserts that one of skill may isolate the requisite sequences or parts thereof by utilizing customary hybridization methods or by PCR, and by virtue of histidine box sequences. Applicant's preceding assertions may be correct, but the central issue is not whether methods are known for identifying sequences having percent homology or similarities to a known sequence. Rather, the issue is whether at time of invention, the species encompassed by the instant genus claims were adequately described in the specification (or were conventional in the art) and whether any disclosed species fairly represent the variation within the entire genus/subgenus to which the claims are directed.

Based on the disclosure and/or the relevant evidence in the art at the time of invention, the artisan cannot predict the operability or interchangeability of a representative number of species, because identification of derivative sequences or sequences having the recited level of homology over a localized region of SEQ ID NO: 2 would not correspond to structures sufficient to provide functional proteins. In other words, merely identifying sequences as being homologous does not automatically suggest that said sequences are sufficient for the requisite enzymatic function. In this regard, the instant disclosure is deficient because merely providing a means to identify sequences (whether nucleic acid or polypeptide derivatives) does not equate to possession of a sufficient number of embodiments.

The artisan could not use computer algorithms or other similar means to envision which of the vast number of identified homologous species actually contains the prescribed activity. For example, if Applicant's assertion is held to be true, given the level of disclosure in the

specification, then any sequence derived from SEQ ID NO: 1 or any sequence identified with 85% homology over any partial sequence of SEQ ID NO: 2 should be sufficient for the requisite enzyme function or activity. Neither the disclosure or the evidence in the art support this assertion.

The disclosure does not characterize a correlation between any common structures (i.e., sequence variants/fragments) that are encompassed within SEQ ID NOs: 1 or 2, as related to the corresponding function, i.e., D6D enzyme activity (e.g., common structures clarified through mutagenesis and biochemical studies so as to identify the critical structural elements). The only disclosure is the full-length nucleic acid (cDNA) and the corresponding polypeptide. It may be true that the disclosed D6D contains certain motifs (i.e., histidine boxes) common to other D6Ds, as Applicant suggests as a means to identify derivatives having the recited relationship to SEQ ID NOs: 1 and 2. (Brief, p. 4, ¶ 1.). It is unclear whether Applicant is asserting that the conserved histidine boxes alone are sufficient to confer the requisite activity. Neither the specification nor evidence in the art suggests that the histidine boxes are sufficient for enzyme function. In any event, the claims are not directed to derivatives having the recited homology over the full-length protein, but over localized *polypeptide sequences*.

Furthermore, the key issue is the identity of derivatives or partial sequences that contain the structural domains that are sufficient D6D activity. The evidence in the art does not support the assertion that conserved histidine boxes provide the enzymatic structural components. (e.g., Sayanova et al. 2000; 28 :636-38, p. 636, col. 1, ¶ 2, regarding borage D6D indicating that it is disruption of the cytochrome b_5 domain that results in non-functional enzyme, as evidenced through site directed mutagenesis).

Therefore, it appears that variations of even a single amino acid residue may have functional implications for a particular D6D, whether within or without the conserved histidine domains. (Id.). For example, in the context of the instant claims, a derivative or fragment can meet the claimed limitation of having at least 85% homology to a particular sequence shown in SEQ ID NO: 2, but may be missing the critical or essential residue necessary to function as a D6D enzyme (e.g., variation of a single amino acid residue outside the conserved histidine box(es)). In addition, variations that would occur with respect to any sized fragment would affect the secondary and tertiary structure of the polypeptide thus affecting the folding properties of said polypeptide. (Hongsthong et al. Appl. Microbiol. Bioteh. 2004; 66:74-84; teaching a *Spirulina* D6D that comprises three histidine motifs, but that also contains additional histidine residues found to be critical for catalytic activity, as well as residues independent of the histine motifs altogether, at p. 83, col. 1, ¶3). As such, even in derivatives that comprise one or all of the histidine boxes, the polypeptide may not inhere the proper folding sufficient to preserve enzymatic function.

With respect to identification of functional domains, the evidence in the art does not suggest that D6D from *P. patens* or D6Ds from other organisms have been characterized to such a level so as to conclude that it is routine and conventional to determine whether a derivative polypeptide retains enzymatic function. (Supra, Hongsthong et al. Appl. 2004). This suggests that derivatives encompassed by the claimed genus would not function interchangeably. Put another way, one of skill would not be apprised of the particular amino acid residues that can be added/omitted or that would be present in derivative sequences of any size, and that would retain enzymatic function. Moreover, the secondary and tertiary structure of proteins (i.e., native

folding) can be altered altogether, for example, by a single amino acid variation in conserved or for that matter variable regions of a protein. For example, the single residue variation does not have to occur in the conserved histidine box regions, but can still affect the folding structure of the polypeptide, which in turn can affect the enzymatic activity. In other words, a structure to function correlation cannot be predicted based on homology analysis alone or the presence of certain conserved domains, where it is unclear whether the conserved domains are sufficient for enzymatic activity. Thus, merely identifying homologous derivative sequences does not necessarily equate to possession of sufficient species within the claimed genera.

As further evidence in the art teaches, to attempt to predict activity based on homology is unpredictable at best. (See, Berendsen. Science. 1998; 282:642-3; indicating that accurate prediction of activity cannot be based on primary structure alone). Furthermore, one of skill would recognize that it is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences, which is further complicated by the modular nature of many proteins. (Attwood. Science. 2000; 290: 471-3, p. 472, col. 2). Additional factors that also complicate functional assignment include: redundancy, nonorthologous displacement replacing genes with unrelated but functionally analogous genes, horizontal gene transfer introducing gene from different phylogeneic lineages and lineage-specific gene loss eliminating ancestral genes. (Id.). Moreover, assessing the actual power of the context based method for protein function prediction, such as that based on homology, requires extensive testing by labor-consuming, case-by-case experimental analysis. (See, Galperin et al. Nat. Biotech. 2000; 18:609-13).

In sum, based on the evidence in the art suggesting variations in sequences encoding an a D6D (e.g., down to a single amino acid residue) can determine enzyme functionality, given the tremendous number of embodiments encompassed by the claims and given the lack of disclosure of any representative embodiments, one of ordinary skill in the art could not envisage a sufficient number of the species to describe the broadly claimed genus/subgenus. Thus, applicant cannot be deemed to be in possession of the claimed genus of nucleic acid derivatives encoding any sized polypeptides and having the requisite enzyme activity.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expressing the Δ6-desaturase of SEQ ID NO: 2 in a plant or algae, does not reasonably provide enablement for expressing the Δ6-desaturase or derivatives/fragments thereof in an animal.**

This is a new ground of rejection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The claims are interpreted consonant with what is stated above.

The test for enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir.

1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are of vast scope and breadth in several different aspects. First, the claims are broad in that they are drawn to methods of altering *any organisms* fatty acid metabolism my expressing *any nucleic acid derivative* encoding a polypeptide sequence corresponding to any amino acid sequence shown in SEQ ID NO: 2, where said polypeptides have at least 85% homology to any of the amino acid sequences shown in SEQ ID NO: 2. Furthermore, additional claims are delimited to expression in *any* plant, algae or oilseed crop. In addition, the claims are similarly broad where directed to virtually any transgenic organism (as recited in base claim 9), into which said nucleic acid derivative are administered to effectuate D6D activity.

Nature of the invention. The invention is directed into heterologous expression of an enzyme isolated from a species of moss (*Physomitrella patens*) in an organism so as to alter the organism's fatty acid metabolism, with the aim of producing unsaturated fatty acids therein.

In addition, with respect to the limitation "mol %" or "% by weight" relative to the unsaturated fatty acid (UFAs) content in an organism, such as a human being, the concentration of said UFAs must be determined, subsequent to introduction of the inventive nuclei acid molecules and expression of the polypeptides encoded therefrom. In other words the methods require a determination of UFA content in the context of the whole animal.

State of the art/Unpredictability of the art. Predictability for expression of heterologous D6D enzymes in various organisms depends on what host organism/cells are transformed with a given heterologous D6D. Primarily, with respect to expression across broad species of organisms, particularly expression in higher organisms (e.g., animals), the state of the art is still developing and requires steps/components and elements that are not conventional or routine. There are examples of heterologous expression of D6Ds from different organisms, but are generally limited to expression in plants and microorganisms, whereby expression of desaturases is targeting fatty acid metabolism therein. (e.g., Reddy et al. Nat. Biotech. 1996; 14: 639-42 (teaching expression of D6D from a cyanobacteria in a tobacco plant – *Nicotania tabacum*); Sakuradani et al. Biosci. Biotech. Biochem. 2003; 67:704-11 (teaching expression of a D6D from one filamentous fungus in another filamentous fungus); Sayanova et al. J. Exp. Botany, 2001; 52: 1581-5 (teaching expression of a plant D6D in yeast); supra, Hongsthong et al, 2004 (teaching expression of a D6D from cyanobacterium in *E. coli*); Laoteng et al. Biochem. Biophys. Res. Comm. 2000; 279: 17-22 (teaching expression of D6D from a fungus in yeast – *C. cerevisiae*); Spychalla et al. Proc. Natl. Acad. Sci. 1997; 94: 1142-1147 (teaching expression of a potential Δ5-desaturase from *C. elegans* in *A. thaliana*)).

Therefore, most of the evidence at the time of invention appears to be directed to expression of D6D in lower plants/microorganisms, with a dearth of relevant teachings of expressing D6Ds from lower organisms in animals. As such, the evidence does not support the assertion that it would be routine to express heterologous D6D (i.e., from *P. patens*) in higher organisms, such as animals (e.g., D6D from *P. patens* in mice, human, etc.).

D6Ds from moss or bacteria do not appear to share a great deal of sequence identity with higher order animals. For example, even as compared to more closely related organisms, D6D from *P. patens* shares very low sequence identify with D6D from said organisms. (Girke et al. Plant J. 1998; 15: 39-48, at p. 39, col. 2, last ¶). Furthermore, most of the evidence in the art is directed to expression of desaturase in oilseed crops so as to produce a wide variety of unusual fatty acids in transgenic crops. (e.g., Kinney et al. Biochem. Soc. Trans., 2002; 30:1099-1103). Notwithstanding the sequence similarity amongst various D6Ds, it is an entirely different proposition to express a heterologous protein in a bacteria or plant, versus expressing in an animal.

There would be a great deal of unpredictability in expressing either full length D6D (i.e., SED ID NO: 2) or derivative and partial fragments thereof in animals, where the aim is to alter the host organisms fatty acid metabolism. For example, expression in an animal with a competent immune system could have adverse outcomes, which include immunotoxicity. Additional unpredictability would result from insufficient or transient D6D expression, as well as potential genotoxicity (e.g., integration into non-target regions or immune response to a particular vector utilized to deliver the nucleic acids encoding D6D, e.g., D6D incorporated in a retroviral vector).

Moreover, with respect to expression of nucleic acid variants of SEQ ID NO: 1 or variants encoding polypeptides sharing the recited level of identity to SEQ ID NO: 2, there would be an additional level of unpredictability as to the polypeptides actually functioning as D6D, as explained in regard to issues dealing with lack of sufficient Written Description. (Supra, Rejection No. 3). In other words, it logically follows that if various embodiments within the

genus of derivatives of *P. patens* D6D would operate unpredictably, then even if the preceding adverse outcomes were obviated (e.g., immunotoxicity), there is additional unpredictability with respect to interchangeability of various derivatives of the claimed D6D (SEQ ID NO: 2) and whether said derivatives are sufficient to function as a D6D enzyme.

In addition, determining molar concentrations of unsaturated fatty acids (UFA) for whole organism can be problematic for higher organisms. For example, while determining said concentration for seeds from a rapeseed plant is routine, determining said concentration for an animal is not. Indeed there do not appear to be any teachings in the art that demonstrate processing a whole animal to determine its UFA concentration (e.g., usual estimations are based on plasma levels or tissue biopsy). Therefore, it is unclear how one of skill would practice the claimed method within the claims' literal scope (i.e., claims 1 and 7) without undertaking unconventional method steps. In sum, making and using the invention as to the full scope of the claims entails unconventional steps and components that make the recited outcomes unpredictable.

Amount of guidance provided. The specification provides generic guidance on how to identify homologous sequences. However, there is no substantial relevant guidance as to what portions of the disclosed sequence (i.e., SEQ ID NOs: 1 and 2) correspond to functional domains. Furthermore, there is no substantial or relevant guidance provided as to heterologous expression of *P. patens* D6D or derivatives thereof in disparate species of organisms, including all animals.

In addition, there is no substantial or relevant guidance provided on how one of skill would culture an animal and with respect to the whole animal determine mol% or total fatty acid

content in an animal. For example, in lieu of a liver biopsy or plasma concentrations, it is unclear whether one would have to "liquefy" the entire animal, including a human being. It is unclear how, the terms "Mol%" and "% by weight", which are terms of art related to plant (e.g., seeds) or microorganisms (e.g., yeast), are to be applied to whole animals, including humans.

Number of working examples. The examples are limited to expressing the protein encoded by SEQ ID NO: 1 (i.e., amino acids of SEQ ID NO: 2), in yeast and plants (e.g., *A. thaliana*). No other relevant examples are provided in expressing the D6D or derivative thereof in any other organism. Further, no relevant examples are provided for expressing derivatives/partial fragments in yeast or plants.

Amount of Experimentation Required. The level of skill in the art required to practice the claimed invention is high. However, given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples relative to the genera of nucleic acids claimed, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention. It should be noted that none of the instant claims are directed to the allowable scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. **Claims 1-4 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Girke et al. (Plant J. July 1, 1998[2]; 15(1): 39-48; see entire document; hereinafter "Girke").**

This is a new ground of rejection. The claims are interpreted consonant with the interpretations stated in the foregoing objection/rejections.

Girke et al. teach identification and expression of a D6D from *P. patens* (PPDES6). (e.g., Abstract). At minimum the reference teaches sequences that are derivatives of SEQ ID NO: 1 or encoding polypeptides that share at least 85% sequence identity with sequences shown in SEQ ID NO: 2. (e.g., Figure 1; depicting PPDES6). Furthermore, the reference teaches that the cDNA for PPDES6 is 2012 bp, i.e., SEQ ID NO: 1. (e.g., p. 40, col. 1, last full ¶). The amino acid sequence disclosed for PPDES6 is the same as that of SEQ ID NO: 2 (Id.).

In addition, the reference teaches expression of PPDES6 in *S. cerevisiae*. (e.g., p. 45, col. 2, ¶ 3; claims 1, 4, 9). Furthermore, expression of PPDES6 in the cells (i.e., cultured cells) produces concentrations of unsaturated fatty acids (i.e., % total) that are at least 1 or 5%, whereby to measure the concentration of said fatty acids, each would have to be isolated from the yeast cells in the first place. (e.g., p. 45, col. 1, Table 1; claims 1, 7-8). Additionally, PPDES6 is from *P. patens*, a moss, which in turn is a plant. (claims 2-3).

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

[2] The document recites "July 1998", but upon contacting the publisher, the date is clarified to mean July 1, 1998.

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. **Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girke et al. (Plant. J. 1998; 15:39-48), either alone or further in view of Napier et al. (Curr. Opin. Plant Bio. 1999 April; 2: 123-27).**

This is a new ground of rejection. The claims are interpreted consonant with what is stated above. Further, the teachings of Girke are incorporated and applied herein consonant with what is stated above. In sum, Girke teaches expression of a D6D isolated from *P. patens* (PPDES6) in yeast cells.

The reference does not teach expression of PPDES6 in plant or oil crop. However, the reference implies that the desaturase, such as PPDES6 isolated from moss, is a good source for producing a wider variety of polyunsaturated fatty acids (UFAs). (e.g., p. 39, under "Introduction"). In any event, utilization of D6Ds to modify the lipid composition in oilseed crop was a primary focus in the art at the time of invention. For example, Napier et al. discuss utilizing desaturases from different sources for producing a wider variety and beneficial UFAs.

(e.g., Abstract; p. 123). More particularly, the reference explicitly notes that the D6D isolated from *P. patens* is another D6D, in the same vein as producing fatty acids in transgenic oilseed crop. (e.g., p. 125, ¶ 1). The primary thrust of Napier et al. is that expression of desaturases in transgenic plants will lead to production of 'designer oil[s]' in said plants so as to meet the demands of the pharmaceutical and chemical industry. (e.g., p. 126, last ¶).

Therefore, it would have been obvious to utilize the PPDES6 desaturase as taught by Girke in plants or oilseed crop. One would have been motivated to make such transgenic plants and to produce UFAs therein, so as to utilize PPDES6, with the benefit of extending the range of beneficial designer oils or UFAs produced. Furthermore, given the level of skill at the time of invention, there would have been a reasonable expectation of success in producing UFAs in a plant, transformed with PPDES6.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER